REMARKS

Entry of the foregoing and further and favorable consideration of the subject application on the merits and in light of the following remarks are respectfully requested.

Claims 24-30 are currently pending. By this amendment, Claim 26 has been canceled, without prejudice to or disclaimer of the subject matter contained therein, and new Claims 35-43 have been added. Claim 24 has been amended to incorporate the limitations of Claim 26. New Claims 35-37 reflect Claims 28-30 rewritten in independent form. New independent Claims 38 and 41 represent previous Claim 24 incorporating the limitations found in current claims 29 and 30, respectively. New dependent Claims 39, 40, 42, and 43 incorporate the limitations of previous claims 25 and 26. Accordingly, no new matter has been added.

Claims 28-30 were previously deemed allowable by the Examiner, if rewritten in independent form. Accordingly, Applicants respectfully submit that at least new Claims 35-37 are in condition for allowance. Additionally, Applicants respectfully submit that Claims 24, 25, 27-30, and 38-43 are also in condition for allowance for the reasons discussed below.

Rejections Under 35 U.S.C. § 103

Claims 24-27 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Kontinen et al. (WO 94/19471) and Highlander et al. (U.S. Patent No. 6,180,112). The Examiner maintains that Kontinen et al. disclose a method for enhancing the secretion of homologous and heterologous bacterial exoproteins, including the use of multicopy

plasmids. The Examiner argues that Highlander et al. disclose the use of whole cell vaccine compositions which overexpress a homologous leukotoxin antigen. The Examiner argues Highlander et al. disclose the use of heterologous antigens in addition to the overexpressed homologous antigens and the use of an attenuated strain of a gram-negative bacteria. Thus, the Examiner concludes that it would have been obvious to use multicopy plasmids to introduce homologous and heterologous antigens into attenuated or avirulent bacteria and administer the bacteria as a vaccine. Claim 26 has been canceled by the present amendment, thereby mooting this rejection as it applies to this claim. This rejection, to the extent that it applies to Claims 24, 25, and 27 and as it may apply to new independent Claims 38-43, is respectfully traversed.

In order to establish a case of *prima facie* obviousness under 35 U.S.C. § 103, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. § 2142. Applicants respectfully submit that the Examiner has not met these criteria.

Independent Claims 24, 27, 38 and 41 require a) extracting DNA from the pathogenic micro-organism, b) obtaining a gene encoding an antigen that stimulates protective immunity, c) inserting the antigen gene into a multicopy plasmid, d) transforming an attenuated or avirulent strain of the pathogenic microorganism, and e) administering an effective amount of the vaccine (attenuated or avirulent strain overexpressing the homologous antigen) to a vertebrate. Claim 24 requires that the

pathogenic micro-organism is *Brucella, Mycobacterium,* or *Vibrio*. Claim 27 further requires that the pathogenic micro-organism is one of four particular *Brucella* species. Independent Claim 38 requires that the at least one gene is a Cu/Zn SOD gene. Independent Claim 41 requires that the at least one gene is one or both of a GroES and a GroEL gene. Applicants respectfully submit that each and every one of these elements of the presently claimed invention are not found in the Kontinen et al. or Highlander et al. publications, either alone or in combination.

With regard to independent Claims 24 and 27, the Examiner argued that Kontinen et al. disclose a method that could be used with:

> any desired exoprotein, ... capsule, outer membrane and fimbria proteins from any Gram-negative bacteria, including M. tuberculosis, Vibrio cholerae. ... any protein toxins or secreted proteins from bacteria, surface proteins of any micro-organisms and antigen proteins or viruses may be overexpressed in the same manner as taught in the reference. Accordingly, this would include *Brucella* as recited in instant claim 27.

(Official Action mailed November 19, 2002, page 3). Applicants respectfully submit that this analysis by the Examiner is an obvious-to-try approach and does not provide the motivation required by 35 U.S.C. § 103. Kontinen et al. merely assert that their method could be broadly applied for generating large amounts of antigenic protein from any bacteria using the **gram-positive expression system**. Applicants respectfully submit that this is insufficient to render obvious the selection of three particular genuses of bacteria out of an extremely large number of possibilities for application in a different method, *i.e.*, that found in Claims 24 and 27. Additionally, as noted above, Kontinen et al. are using gram-positive bacteria for overexpression. That is, while Kontinen et al. suggest that antigenic

proteins of *Mycobacterium* and *Vibro* might be used in their method, this would be **heterologous** overexpression, not **homologous** overexpression achieved in the presently claimed invention. Applicants respectfully submit that this suggestion by Kontinen et al. is irrelevant to the presently claimed invention. The fact that Kontinen et al. blanketly suggest that any bacteria can be used in their heterologous system is not sufficient to render obvious the choice of three particular gram-negative bacteria in a homologous overexpression vaccine as in the presently claimed invention.

Moreover, Claim 27 also limits the particular genus of *Brucella* to four particular species. The Examiner has not provided any concrete evidence of motivation in either the Kontinen et al. (other than a sweeping statement that "any bacteria" necessarily includes *Brucella*) or Highlander et al. publications that points the skilled artisan towards *Brucella*, or the particular species of *Brucella* claimed. Accordingly, neither the Kontinen et al. nor the Highlander et al. publications can render independent Claim 27 obvious.

Applicants respectfully direct the Examiner's attention to the claims of U.S. Patent No. 6,149,920, the parent application of the present application, which was also examined by the present Examiner. A copy of the '920 patent was submitted with the response filed February 5, 2003. Independent Claim 1 of the '920 patent is directed toward a vaccine, which the Examiner will observe could be produced and utilized according to the method of Claims 24 or 27, for immunization, prophylaxis, or treatment of Brucellosis.

With regard to new independent Claims 38 and 41, Applicants respectfully submit that the Examiner has not provided any evidence or motivation, and Applicants know of none, in either the Kontinen et al. or the Highlander et al. publications that would lead one

skilled in the art to homologously overexpress a Cu/Zn SOD gene, a GroES, or a GroEL gene to generate a attenuated or avirulent vaccine. Thus, Applicants respectfully submit that Claims 38-43 are not rendered obvious by the Kontinen et al. or Highlander et al. publications.

Applicants respectfully submit that the above comments demonstrate the non-obviousness of the presently claimed invention. The Examiner has not demonstrated that either the Kontinen et al. or the Highlander et al. publication, either alone or in combination, disclose or suggest each and every element of independent Claims 24, 27, 38, and 41. Additionally, the Examiner has pointed to no motivation, either in the two cited publications or elsewhere, that would lead one skilled in the art to the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Applicants respectfully submit that all pending claims 24, 25, 27-30, and 35-43 are in condition for allowance.

Conclusions

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Jennifer Topmiller
Jennifer A. Topmiller, Ph.D.
Registration No. 50,435

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: March 18, 2003

Attachment to Reply and Amendment dated March 18, 2003

Marked-up Claim 24

24. (Three Times Amended) A method for immunization, prophylaxis or treatment of a vertebrate at risk of or suffering from a disease caused by a pathogenic micro-organism comprising the steps of:

a) extracting deoxyribonucleic acid from the pathogenic micro-organism;

b) identifying at least one gene encoding at least one antigen from the deoxyribonucleic acid, wherein said at least one antigen is capable of stimulating protective immunity against the pathogenic micro-organism;

c) inserting the at least one gene into a multicopy plasmid capable of replicating and expressing in the pathogenic micro-organism;

d) transforming an attenuated or avirulent strain of the otherwise pathogenic micro-organism with the plasmid to form a vaccine; and

e) administering an effective amount of said vaccine to the vertebrate,

wherein the pathogenic micro-organism is selected from the group consisting of *Brucella*, *Mycobacterium*, and *Vibrio*.